UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

ALLERGAN, INC.,	)	
Plaintiff,	)	
v.	)	**Civil Action No. 03-2236 (RMC)**
LESTER M. CRAWFORD, DVM, Ph.D., Acting Commissioner of Food and Drugs, and TOMMY G. THOMPSON, Secretary, Health and Human Services,	)	
Defendants.	)	

MEMORANDUM OPINION

This lawsuit arises from a dispute over the Food and Drug Administration's ("FDA") classification of cyclosporine as an "antibiotic" drug. Allergan, Inc. ("Allergan") is a pharmaceutical company that manufactures Restasis®, a 0.05% topical ophthalmic emulsion of cyclosporine that is used to treat an eye condition known as keratoconjunctivitis or dry eye disease. Allergan argues that cyclosporine is not an "antibiotic" drug because the substance actually suppresses the human body's immune system, making the patient more and not less susceptible to microbial infection. Consistent with its decision in *CollaGenex Pharm., Inc. v. Thompson*, No. 03-1405 (D.D.C. January 19, 2005) ("*CollaGenex*"), the Court finds that the FDA classification decision is supported by the Food and Drug Modernization Act of 1997 ("FDAMA"), Pub. L. No. 105-115, 111 Stat. 2296, and the administrative record. The complaint will be dismissed.[1]

[1] Dr. Crawford has been substituted for Mark B. McClellan, M.D. Ph.D., as a defendant pursuant to Federal Rule of Civil Procedure 25(d)(1).

I. BACKGROUND FACTS

Allergan first contacted FDA about Restasis in December 1998, when it requested a number to submit a New Drug Application ("NDA") for FDA review and approval. FDA's Center for Drug Evaluation and Research ("CDER") assigned number 21-023, which is the number used by Allergan on its NDA request submitted on February 24, 1999. FDA approved the NDA on December 23, 2003. AR Tab 7.[2]

As described in greater detail below, the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. §§ 301-397, as amended, provides patent protection and exclusive marketing for certain drugs. These protections deny FDA the authority to approve a generic version of the drug for the period of three or five years, depending on the degree of innovation reflected in the NDA. The distinction between drugs entitled to market exclusivity/patent protection and those not so entitled, depends on whether the drug is classified as an "antibiotic" that was subject to FDA review prior to 1997. Allergan's NDA requested that Restasis be approved as a non-antibiotic drug, which would protect it from generic competition. *See* Compl. ¶ 37. However, after approving Restasis, the FDA notified Allergan that Restatis was ineligible for these protections because its active ingredient, cyclosporine, is classified as an "antibiotic." FDA advised Allergan of this determination by telephone and memorialized the decision in a letter to Allergan dated March 3, 2003. AR Tab 8. That letter also assigned Restasis a new NDA number, 50-790, to correspond to its "antibiotic"

[2] The administrative record was submitted in two parts: the first constitutes the record of FDA's decision that cyclosporine is an "antibiotic" and the second constitutes the record of FDA's consideration of Allergan's citizen petition to have Restasis reclassified. The latter encompasses the former and will be the record to which the Court refers.

drug status. *Id.*

Through a citizen petition submitted to FDA on June 16, 2003, Allergan requested that FDA reclassify cyclosporine as a "non-antibiotic drug" and remove it from the list of drugs that are ineligible for marketing exclusivity and patent listing. AR Tab 9 at 1. On August 1, 2003, Allergan filed a petition for a stay of approval of all generic versions of Restasis until the FDA had ruled on the citizen petition. Allergan instituted this lawsuit on October 31, 2003. On December 18, 2003, FDA denied Allergan's petition.

II. STATUTORY SCHEME

Prior to 1997 and the passage of the FDAMA, "antibiotic" drugs were approved under Section 507 of the FFDCA, 21 U.S.C. § 357 ("Section 507"), and non-antibiotic drugs were approved under Section 505, 21 U.S.C. § 355 ("Section 505"). This difference had a long history, dating back to the development of penicillin, the first drug to have the capacity to kill microbes, *i.e.*, be "anti-biotic." Because penicillin was manufactured in batches through fermentation, its strength and efficacy could vary depending on the rigor of that process.[3] Congress required that FDA test all batches of penicillin to ensure that appropriate doses were administered to the military during World War II. Initially, Section 507 applied only to penicillin or any derivative of penicillin; other named antibiotic drugs were added to the statute as they were developed.[4] When the FFDCA was amended

[3] *See* H.R.REP. NO. 79-702 at 2-3 (1945) ("A primary reason for the type of control proposed by this bill is the fact that penicillin is produced by a biological process and is subject to the vagaries inherent in all such processes."). FDA stopped requiring batch certifications for many antibiotic drugs in 1982. 47 Fed. Reg. 39155 (Sept. 7, 1982); *see also*, 21 C.F.R. § 433.1 (1983).

[4] Streptomycin was added in 1957; aureomycin, chloramphenicol, and bacitracin were added in 1949; chlortetracycline was substituted for aureomycin (a trade name for chlortetracycline) in 1953. Roeder Mem. at 5 n.6.

in 1962, a more generalized definition was added so that the law would not need amending with each new discovery of an antibiotic drug.[5]

Two key consequences arose from these different treatments. Applicants for generic versions of antibiotic drugs were only requested to show conformance with statutorily-mandated, published standards of identity, strength, quality, and purity for the antibiotic substance, as reflected in antibiotic "monographs" published by FDA. Pharmaceutical companies did not have to submit the safety and efficacy data that was required for pioneer and generic non-antibiotic drugs. Therefore, generic antibiotics were developed and marketed fairly readily. *See Glaxo, Inc. v. Heckler*, 623 F. Supp. 69, 72 (E.D.N.C. 1985); Abbreviated New Drug Applications, Proposed Rule, 54 Fed. Reg. 28872, 28878 (July 10, 1989). However, antibiotic drugs did *not* receive the patent listing, patent certification, and marketing exclusivity benefits available to pioneer and non-antibiotic drugs after enactment of the Drug Price Competition and Patent Term Restoration Act ("Hatch-Waxman"), Pub.

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[5] *See* Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780, amending 21 U.S.C. § 357 to read:

> The Secretary, pursuant to regulations promulgated by him, shall provide for the certification of batches of drugs (except drugs for use in animals other than man) composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chlorampenicol, bacitracin, or any other antibiotic drug, or any derivative thereof. A batch of any such drug shall be certified if such drug has such characteristics of identity and such batch has such characteristics of strength, quality, and purity, as the Secretary prescribes in such regulations as necessary to adequately insure safety and efficacy of use, but shall not otherwise be certified . . . . For purposes of this section . . . , the term 'antibiotic drug' means any drug intended for use by man containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution (including the chemically synthesized equivalent of any such substance).

21 U.S.C. § 357(a) (repealed) (AR Tab 24).

L. No. 98-417, 98 Stat. 1585 (1984).

A. Hatch-Waxman Amendments

The significance of the Hatch-Waxman Amendments to FFDCA cannot be understated. Prior to 1984, all applicants seeking to market pioneer drugs or generic non-antibiotic drugs had to file an NDA containing, *inter alia*, extensive scientific data demonstrating the safety and effectiveness of the drug. *See* 21 U.S.C. § 355(a)-(b); 21 C.F.R. § 314.50. As a result, few generic non-antibiotic drugs were approved by FDA. *See Glaxo*, 623 F. Supp. at 72. Hatch-Waxman created an abbreviated approval process for generic non-antibiotic drugs, while retaining incentives for pioneer drugs, such as marketing exclusivity and patent protections. *See* 21 U.S.C. § 355(jj). The abbreviated new drug application ("ANDA") process shortens the time and effort needed for approval of a generic drug by allowing the applicant to merely demonstrate its product's bioequivalence to the NDA drug, without reproducing the entirety of the NDA's extensive scientific research. *See Eli Lilly and Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990) (describing the ANDA process).

Because Congress still wanted to provide incentives for new drug development, alongside the ANDA process that eased the marketing of generic drugs, Hatch-Waxman entitles an NDA applicant to a period of market exclusivity (3 or 5 years, depending on the degree of innovation reflected in the NDA) which bars FDA approval of a generic ANDA for the NDA product. *See* 21 U.S.C. § 355 (c)(3)(D)(ii)-(iv), (j)(5)(D)(ii)-(iv). In addition, an NDA applicant must inform FDA about any patent that the NDA applicant claims will protect its exclusivity to market its drug. 21 U.S.C. § 355(b)(1), (c)(2). FDA then publishes patent information for approved drugs in the "Approved Drug Products With Therapeutic Equivalence Evaluations" (the "Orange Book"). *See*

21 U.S.C. § 355 (b)(1), (c)(2), (j)(7); 21 C.F.R. §314.53(e). Generic drug manufacturers check the Orange Book to determine if a drug product is patent-protected or if it is available for the development of a generic bioequivalent drug.

An ANDA applicant must certify to FDA that (I) patent information has not been filed; (II) the patent has expired; (III) the patent will expire shortly on a date certain; or (IV) the patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug covered by the application. 21 C.F.R. § 355(j)(2)(A)(vii). Under a paragraph IV certification, the applicant must also notify the NDA holder and patent owner concerning its application and its reasoning for applicability of paragraph IV. 21 U.S.C. § 355(b)(2)(B), (j)(2)(B). The filing of a paragraph IV certification "for a drug claimed in a patent or the use of which is claimed in a patent" is an act of infringement. 35 U.S.C. § 271(e)(2)(A). The holder of the patent for the drug may therefore initiate a patent infringement suit upon the ANDA applicant; if it does so, FDA will stay approval of the ANDA application for 30 months, unless a final court opinion is reached earlier, or for the term ordered by the patent court. 21 U.S.C. § 355(c)(3)(C), (j)(5)(B)(iii). It is these protections from early competition for which Allergan sues.

B. FDAMA

When Congress adopted FDAMA in November 1997, it repealed Section 507 of the FFDCA and required that all applications for antibiotic drugs be submitted under Section 505. FDAMA § 125(d)(1) (Transition). In subsection (d)(1), the Transition provided that applications for antibiotic drugs approved under Section 507 before FDAMA would be considered approved under Section 505. *Id.* However, subsection (d)(2) added the provision that when "the drug that is the subject of the application contains an antibiotic drug and the antibiotic drug was the subject of any

application" received by FDA before the enactment of FDAMA, it is exempt from Hatch-Waxman benefits. FDAMA § 125(d)(2); Proposed Rule: Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs, 65 Fed. Reg. 3623, 3624-25 (Jan. 24, 2000); Section 507 Repeal Guidance at 2. Specifically, § 125(d)(2) exempts from Hatch-Waxman:

> any application for marketing in which the drug that is the subject of the application contains an antibiotic drug and the antibiotic drug was the subject of any application for marketing received by the Secretary of Health and Human Services under section 507 of such Act (21 U.S.C. § 357 [Section 507]) before the date of enactment of this Act.

Pub. L. No. 105-115, 111 Stat. 2327 (1997), § 125(d)(2) (*reprinted in* 21 U.S.C.A. § 355 Historical and Statutory Notes, "Transition"). Antibiotic drugs that were the subject of pre-FDAMA applications are known as "old antibiotics" and will be so referenced here.

With the enactment of FDAMA in 1997, Congress moved the definition of an "antibiotic" drug to 21 U.S.C.§ 321(jj). The law defines an antibiotic drug as:

> any drug (except drugs for use in animals other than humans) composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other drug intended for human use containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution (including a chemically synthesized equivalent of any such substance) or any derivative thereof.

21 U.S.C. § 321(jj).

III. THE ADMINISTRATIVE RECORD

Allergan submitted an NDA to FDA on February 24, 1999, for approval of Restasis (cyclosporine ophthalmic emulsion) Ophthalmic Emulsion, 0.05%, as a non-antibiotic drug under Section 505 of the FFDCA. AR Tab 7. It received approval from FDA dated December 23, 2002, as a non-antibiotic drug. *Id*. However, on March 3, 2003, FDA sent a second letter to Allergan, in

which it noted the repeal of Section 507 by FDAMA and the FDA's listing of the "active drug substances" that were approved before FDAMA, and were therefore affected by the exemption from Hatch-Waxman protections under Section 125(d)(2).[6] In this roundabout fashion, FDA informed Allergan that it was reclassifying Restasis as an "antibiotic" drug because it contains cyclosporine, a drug previously approved by FDA for marketing prior to FDAMA.

Restasis is not approved for any antibiotic use. In fact, the packet insert for Restasis "states that it 'is contraindicated in patients with active ocular infections.'" Allergan Motion for SJ at 11. FDA did not provide any written explanation of its decision to reclassify Restasis in 2003 other than the oblique reference to the listing of cyclosporine as a pre-FDAMA approved drug. The issue thus becomes whether cyclosporine was properly classified as an antibiotic.

The Administrative Record reflects the FDA's initial classification of cyclosporine as an "antibiotic" drug in 1983 in connection with Sandimmune® and a subsequent version, Neoral® (drugs to suppress organ rejection in transplant patients) upon which FDA relies in classifying Restasis as an "antibiotic." Sandoz Pharmaceuticals, Inc., submitted its NDA for Sandimmune in July 1982 and received approval from FDA under Section 507 as an antibiotic drug on November 14, 1983. AR Tabs 1 & 2. Thereafter, it appears that Sandoz submitted additional NDAs for Sandimmune Rheumatoid Arthritis (oral solution and soft gelatin capsules) on February 28, 1994, as a non-antibiotic drug.[7] Sometime after the approval of the 1994 applications, Charles

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[6] The FDA referred Allergan "to the *Federal Register* notice 99N-3088, *Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs* issued January 24, 2000, which lists the active drug substances, including any derivative thereof, that are directly affected by the repeal of Section 507." AR Tab 8.

[7] *See* Attachment 1 to Motion for Order Requiring Addition of Documents to the Administrative Record. This Motion is unopposed by the defendants and will be granted. Each

Kumkumian, Ph.D., Assistant Director of Chemistry, FDA Office of Drug Evaluation I and II, reversed the drug status of these NDAs and reclassified them as antibiotics.[8] According to a contemporaneous memo of a telephone conversation between Sandoz and FDA on this reversal, the drug status of Sandimmune "had created much internal discussion in Pilot Drug" and "many members in Pilot Drug did not agree nor understand why Sandimmune is classified [as] an antibiotic." Att. 1.

Sandoz objected to the classification of its rheumatoid arthritis drugs as antibiotics and sought to have it changed. In its request for reconsideration, Sandoz argued that the "clinically relevant and valid interpretation" of the statutory language, "in dilute solution" should be that:

> *minimal inhibitory concentrations* (*MIC's*) *of the chemical substance against human pathogens be achievable in human serum, plasma or other relevant body solution* (*e.g.*, *urine*) *following administration of recommended doses of the drug in the target patient population*.
>
> This definition would insure that drugs with *in vitro* antimicrobial activity only at concentrations that cannot be safely achieved and maintained in man would not be inappropriately classified as antibiotics for human use.

AR Tab 3 at 2 ("Ramsey Memo"). As part of its analysis of the arguments presented by Sandoz, the FDA concluded: "After review of the data submitted by the sponsor and that retrieved from the National Library of Medicine database . . . , no credible evidence or rationale was identified that would support the conclusion that cyclosporine has any clinically relevant antibacterial activity."

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of these four documents added to the administrative record will be referred to as "Att. #" hereafter. Attachments A, B and C to the Defendants' Response to Plaintiff's Motion for Order Requiring Addition of Documents to the Administrative Record will also be added to the administrative record.

[8] This after-the-fact reclassification had occurred with the first NDA applications for cyclosporine as well.

Id. at 6. Nonetheless, FDA concluded that "[c]yclosporine has been shown to possess antifungal activity against 2 relevant human pathogens" in *in vitro* and animal studies and "should remain classified as an antibiotic drug." *Id.* at 14. This result was reported to Sandoz, as applicable to three approved NDAs and two pending NDAs, by letter dated April 19, 1995. AR Tab 4.

Novartis, successor to Sandoz, took up the cudgels on March 19, 1997, and sought reconsideration of the classification of cyclosporine. AR Tab 5. It argued that FDA's approach led to inconsistent results because of the lack of standards "subjected to scientific input and critical public scrutiny." *Id.* at 2. Most particularly, Novartis argued that lovastatin, classified as a non-antibiotic, is "obviously similar to cyclosporine in its fungal derivation and antifungal properties." *Id.* More generally, Novartis argued that Congress intended only to treat "true 'antibiotics'" as antibiotics, that is, those drugs used in the treatment of infectious diseases. *Id.* at 3. This letter from Novartis was followed by a letter from "an experimental pharmacologist . . . and a specialist in transplantation infectious disease [retained by Novartis] to review the issue of the classification and potential use of cyclosporine as an antimicrobial agent." Att. 2. After a thorough review of the literature, FDA concluded that "the available data are insufficient to support the conclusion that lovastatin, simvastatin, and prevastatin have sufficient antimicrobial activity [in dilute solution] to warrant their reclassification as antibiotic drugs." AR Tab 6. Having rejected the comparison between cyclosporine and lovastatin, FDA refused to reclassify cyclosporine.

Allergan notes that FDA staff agreed, in an August 1998 meeting with Pharmacia & Upjohn, "that the definition of an 'antibiotic drug' could be interpreted in various ways." AR Tab 16, Att. 11, at 3. This meeting followed a letter from Pharmacia & Upjohn, arguing that FDA's classification scheme was faulty. *See* Att. 3. The letter pointed to two then-recently approved cancer

drugs, Nipent® (pentostatin for injection) and Novantrone® (mitoxantrone for injection concentrate). *Id.* Those two cancer drugs were "listed as antineoplastic antibiotics in the Physicians' Desk Reference" but were regulated by FDA as non-antibiotics. *Id.* While the administrative record here does not address Novantrone further, Allergan also submits a November 8, 1991, letter from Parke-Davis, the sponsor of Nipent, to FDA. Att. 4. In that letter, Parke-Davis submitted data "from a study in which pentostatin was tested in our primary *in vitro* screen" and shown to be inactive. *Id.* Nipent continues to be listed in the index to the current Physicians' Desk Reference as an antineoplastic antibiotic; Novantrone no longer appears in that listing. Motion for Order Requiring Addition of Documents to the Administrative Record at 4.

Allergan's citizen petition was considered in light of this history. Allergan requested that FDA reclassify cyclosporine as a non-antibiotic drug, arguing that cyclosporine is not approved or labeled for "any antibiotic indications." AR Tab 9 at 3. Allergan suggested a "common sense" approach whereby FDA would classify as antibiotics only those drugs that "contain[] at least one approved antibiotic indication" and are "labeled and marketed as an antibiotic." *Id.* at 7-8. Allergan also argued that "FDA should have construed the term 'antibiotic drug'" in Section 125(d)(2) of FDAMA "to mean *antibiotic drug product* rather than antibiotic active moiety." *Id.* at 16.

When FDA rejected Allergan's petition, it took the position that "[t]he statutory definition of antibiotic drug turns on the nature of the drug substance; the definition does not reference a particular quantity of the drug substance, nor a particular indication." AR Tab 39 at 1. At the same time, FDA reviewed the Ramsey Memo, AR Tab 3, which had been generated in response to the Sandoz request for reclassification in 1994.

Dr. Ramsey determined from *in vitro* studies and *in vivo* animal studies that

> cyclosporine has antimicrobial activity against these two fungal pathogens at concentrations that are found in human plasma following the administration of cyclosporine [for non-antibiotic purposes] at its recommended doses in patients. FDA reviewed Dr. Ramsey's 1994 analysis and determined that his conclusion was "based on reasonable factors and a reasonable assessment of those factors."

Defs.' Motion for SJ at 13 (citations to record omitted). FDA also reviewed Dr. Ramsey's 1997 analysis of the classification of lovastatin and again concluded that "at concentrations found in humans treated at the recommended doses of lovastatin and simvastatin (another drug similar to lovastatin that FDA considered in its review), neither of those products had been shown to have the capacity to inhibit or destroy micro-organisms." *Id.*

IV. LEGAL STANDARDS

FDA's decision that Restasis is an "antibiotic" drug under Section 125(d)(2) of FDAMA is subject to review under the Administrative Procedure Act ("APA") and will be reversed only if it is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). This standard is commonly deferential to agency action. *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 416 (1971). When an agency is construing its own organic statute, this deference is at its highest. *Chevron U.S.A., Inc. v. Natural Res. Def. Council*, 467 U.S. 837 (1984); *see also United States v. Mead Corp*, 533 U.S. 218 (2001). "If the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *Chevron*, 467 U.S. at 842-43. If the language of the statute is not clear and unambiguous, a court may not "simply impose its own construction," but must determine whether the agency's construction is a permissible interpretation. *Id.* at 843; *see also id.*, at 843 n.11 (agency's interpretation need not be the only one it could have adopted or even

the one the court would have adopted); *Barnhart v. Walton*, 535 U.S. 212, 218 (2002) (court must decide first, whether statute unambiguously forbids agency interpretation, and second, whether that interpretation exceeds the bounds of permissible); *Mead*, 533 U.S. at 229 (a court cannot reject an agency interpretation that is merely "unwise," if Congress has not spoken clearly and the agency's interpretation is "reasonable"). "The fair measure of deference to an agency administering its own statute has been understood to vary with circumstances, and courts have looked to the degree of the agency's care, its consistency, formality, and relative expertness, and to the persuasiveness of the agency's position . . . ." *Mead*, 533 U.S. at 228 (citing *Skidmore v. Swift & Co.*, 323 U.S. 134, 139-40 (1944)).

The FDA, in particular, is often accorded special deference when its decisions are based on an evaluation of the scientific record before it. "There is no denying the complexity of the statutory regime under which FDA operates, the FDA's expertise or the careful craft of the scheme it devised to reconcile the various statutory provisions . . . . We therefore accord *Chevron* deference to FDA's letter decision here . . . ." *Mylan Labs., Inc. v. Thompson*, No. 04-5296, 2004 WL 2710043, at *6 (D.C. Cir. Nov. 30, 2004). Courts "review scientific judgments of the agency 'not as the chemist, biologist, or statistician that we are qualified neither by training nor experience to be, but as a reviewing court exercising our narrowly defined duty of holding agencies to certain minimal standards of rationality.'" *Troy Corp. v. Browner*, 120 F.3d 277, 283 (D.C. Cir. 1997) (citation omitted). When FDA's interpretation of the FFDCA "rests on 'the agency's evaluations of scientific data within its area of expertise'" it is "entitled to a 'high level of deference' from this court." *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1320 (D.C. Cir. 1998) (citation omitted).

Policy judgments made by an agency within its area of expertise are also entitled to

deference from the courts:

> Such deference, the Supreme Court recently explained, is justified because the responsibilities for assessing the wisdom of policy choices and resolving the struggle between competing views of the public interest are not judicial ones, and because of the agency's greater familiarity with the ever-changing facts and circumstances surrounding the subjects regulated.

Nat'l Rifle Ass'n v. Reno, 216 F.3d 122, 132 (D.C. Cir. 2000) (quoting in part *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 131 (2000) (citations and internal punctuation omitted)).

Even when *Chevron* deference does not apply, the courts will give "considerable and in some cases decisive weight" to an agency interpretation of a statute that is "made in pursuance of official duty, [and is] based upon more specialized experience and broader investigations and information" than a court might have, as long as the decision is carefully and thoughtfully made. *Skidmore*, 323 U.S. at 139-40.

Upon review under the APA, an agency must demonstrate that it "examine[d] the relevant data and [can] articulate a satisfactory explanation for its action including a 'rational connection between the facts found and the choice made.'" *State Farm*, 463 U.S. at 43 (citing *Burlington Truck Lines, Inc. v. United States*, 371 U.S. 156, 168 (1962)). "[T]he court must consider whether the decision was based on a consideration of the relevant factors." *Overton Park*, 401 U.S. at 416. To be sustained, an agency decision must be one that "consider[ed] the relevant factors" and "is within the bounds of reasoned decisionmaking." *Baltimore Gas & Electric Co. v. Natural Res. Def. Council, Inc.*, 462 U.S. 87, 105 (1983). In addition, a "fundamental rule of administrative law" is that a court reviewing an agency decision "must judge the propriety of [agency] action solely by the grounds invoked by the agency." *SEC v. Chenery*, 332 U.S. 194, 196 (1947). Because the court's review "is confined to the administrative record at the time of the agency's decision, it may

not include 'some new record made initially in the reviewing court.'" *Fund for Animals v. Williams*, 245 F. Supp. 2d 49, 54 (D.D.C. 2003) (citations omitted). The courts "do not rely on counsel's *post hoc* rationalization for upholding an agency's action." *McDonnell Douglas Corp. v. Air Force*, 375 F.3d 1182, 1188 (D.C. Cir. 2004); *see also Bowen v. Georgetown Univ. Hosp.*, 488 U.S. 204, 212 (1988) (courts may not accept counsel's post hoc rationalizations for agency orders); *Williams Gas Processing-Gulf Coast Co., L.P. v. FERC*, 373 F.3d 1335, 1345 (D.C. Cir. 2004) ("[*P*]*ost hoc* rationalizations by agency counsel will not suffice.") (quoting *Western Union Corp. v. FCC*, 856 F.2d 315, 318 (D.C. Cir. 1988)).

IV. ANALYSIS

FDA defends its Cyclosporine Decision as compelled by FDAMA and a reasonable interpretation of the statutory definition of "antibiotic" to which the Court must give deference.

A. FDAMA

The Court finds that the statutory command in FDAMA is clear and binding on the FDA and the courts. When "the intent of Congress is clear, that is the end of the matter; for the courts, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *Chevron*, 467 U.S. at 842-43.[9] FDAMA explicitly exempts from the benefits of Hatch-Waxman a drug that "contains an antibiotic drug" when that antibiotic drug was the "subject of any application for marketing" received by FDA prior to the enactment of FDAMA. FDAMA § 125(d)(2). It is clear that cyclosporine was the "subject of an[] application for marketing" prior to FDAMA and that

[9] This conclusion does not rely on deference to FDA. "Deference to an agency's statutory interpretation 'is only appropriate when the agency has exercised its *own* judgment,' not when it believes that interpretation is compelled by Congress." *Arizona v. Thompson*, 281 F.3d 248, 254 (D.C. Cir. 2002) (citations omitted) (emphasis in original).

the FDA has determined that cylosporine is an "antibiotic." If the FDA's determination about the status of cyclosporine is (or was) correct, FDAMA bars Allergan from having Restasis treated as a non-antibiotic. *See CollaGenex*, slip op. at 14.

Allergan does not contest this conclusion. Its argument is that FDA has been arbitrary, capricious and in violation of the FFDCA when it classified cyclosporine as an antibiotic in the first place and retained that classification ever since.

B. The Statutory Definition of "Antibiotic Drug"

While Allergan presents a perfectly plausible interpretation of the definition of "antibiotic" drug based on statements from the legislative history, the contrary interpretation presented by FDA is tied more closely to the actual language of the text.

1. "Intended Use"

Allergan argues that FDA has ignored the congressional intention to define an "antibiotic" drug as one that is intended for the treatment of infectious disease. Allergan Motion for SJ at 18-20. It quotes, among other references, the statement of Secretary Ribicoff, Secretary of the Department of Health, Education and Welfare ("HEW") (now Health and Human Services ("HHS")) when the 1962 law was being considered, to the effect that "antibiotic drugs are drugs of first choice *in treating life-threatening infectious conditions*." Allergan Motion for SJ, Attachment B, 1962 Amendment Hearings, Part 5, at 2590. Allergan notes that FDA has generally applied the antibiotic drug definition to drugs that treat infections. Allergan Motion for SJ at 7. It also notes, without any objection, that FDA has approved some drugs used in the treatment of cancers as antibiotic even though they are too toxic to be used for anti-microbial use. *Id.* However, "there are inadequate human data to show that cyclosporine," the first approved drug to prevent organ rejection by

suppressing the immune system, "has antimicrobial activity in humans." Roeder Mem. at 8. Indeed, no drug product containing cyclosporine has ever been approved for any anti-infective use. Allergan concludes that cyclosporine has been misclassified "for reasons now apparently lost in FDA's prehistory." *Id.* at 7.

The first step in interpreting a statute is, of course, to begin with its words. *Barnhart v. Sigmon Coal Co., Inc.*, 534 U.S. 438, 450 (2002) ("As in all statutory construction cases, we begin with the language of the statute."). The relevant language for this purpose defines an "antibiotic" drug as "any other drug intended for human use containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution . . . ." 21 U.S.C. § 321(jj). Thus, an "antibiotic" is a drug that contains a chemical substance that is [1] produced by microorganisms and [2] has the capacity to inhibit or destroy microorganisms in dilute solution. "[A]ny quantity" of such a chemical substance renders a drug an "antibiotic." Contrary to Allergan's argument, the FFDCA does not limit the *statutory* definition of "antibiotic" drug to only those drugs that fight infections – although most antibiotics *in use* do fight infections. Allergan acknowledges that "[a]pplied literally, [the statute] encompasses products that are neither approved nor marketed for antibiotic indications." AR Tab 9 at 7.

When Congress has chosen to define a category by the product's use or intended effect, it has done so explicitly. *See* 21 U.S.C. §§ 321(g)(1)(B) (drugs), (h) (devices) & (i) (cosmetics); 321(s) & (w) (food additive and animal feed). The only "intended use" language that is found in the definition of an "antibiotic" drug is that it must be intended for human use. Allergan cites the FFDCA definition of "food" as an example of an intended use that is not explicit. *See* 21 U.S.C. § 321(f) (defining "food," in part, as "articles used for food or drink for man or other

animals"). This terminology has already been found not to convey an "intended use" limitation. *Nutrilab, Inc. v. Schweiker*, 713 F.2d 335, 337 (7th Cir. 1983). More significantly, the definition of "antibiotic" drug at Section 321(jj) *does* contain an "intended use" – use for humans – just not the one Allergan would write into the statute – use for infectious disease. "[W]hen 'Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposefully in the disparate inclusion or exclusion.'" *Barnhart Sigmon Coal*, 534 U.S. at 452 (quoting *Russello v. United States*, 464 U.S. 16, 23 (1983)).

In addition, FDA persuasively argues that it has consistently and publicly interpreted "antibiotic" drug to include products whose intended use is not antimicrobial, including: an early letter to a Senator in 1963, AR Tab 16, Attachment 19; various cancer drugs, AR Tab 39 at 15, Tab 16 at 4-5, Tab 21, Tab 28; cyclosporine in 1983 and later, AR Tab 2 & 17; and the immunosuppressant drugs tacrolimus and mycophenolate in 1994 and 1995, *see* http://www.fda.gov/cder/ob/default.htm. In January 2000, FDA listed these cancer drugs and immunosuppressant drugs (including cyclosporine) on the proposed list of "active moieties" of antibiotic drugs that were the subject of marketing applications received by FDA under Section 507 before the enactment of FDAMA. *See* Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs, 65 Fed. Reg. 3623 (Jan. 24, 2000), AR Tab 27.

"[R]eference to legislative history is inappropriate when the text of the statute is unambiguous." *Dep't Housing & Urban Dev. v. Rucker*, 535 U.S. 125, 132 (2002). The text of Section 321(jj) is quite clear on the issue of the intended use of an "antibiotic" drug: such a drug must be "intended for human use" and not "intended for antimicrobial use in humans," as Allergan

would read it. It must be concluded that on this point the statutory language is clear and the definition of an "antibiotic" drug is not limited to drugs whose intended use is to fight infectious disease. *Chevron*, 467 U.S. at 842 ("If the intent of Congress is clear, that is the end of the matter . . . .").

2. "In Dilute Solution"

"Both Allergan and FDA agree that Congress did not specify what it meant by the term 'in dilute solution.'" Defs.' Motion for SJ at 27. "FDA interprets 'in dilute solution' to mean at a concentration that correlates with levels of the antibiotic drug substance expected to be found in human tissue (*e.g.* plasma) at any proposed or approved dose of a drug containing the antibiotic substance." *Id.* at 27-28. "[A] drug will not be classified as an antibiotic drug if the drug contains a chemical substance that has the capacity to inhibit micro-organisms but only at concentrations that are higher than would be achieved by using the drug as proposed or approved." *Id*. at 28. *See CollaGenex*, slip op. at 14-15.

Allergan attacks this definition as "unreasonable" and FDA's methodology for deciding a drug's status arbitrary because it renders a drug's antibiotic status dependent on the order in which NDAs are submitted. In other words, if Restasis were the first drug application using cyclosporine, neither cyclosporine nor Restasis would be classified as antibiotics because the level of cyclosporine in Restasis is insufficient to cause any antimicrobial action in human tissue, *i.e.,* "in dilute solution." Restasis is an "antibiotic" only because an earlier application (for Sandimmune and other immunospressants) used cyclosporine at concentrations high enough to inhibit or destroy microorganisms. Allergan also argues that FDA should not consider *in vitro* and *in vivo* animal studies to decide whether a chemical substance has the capacity to inhibit or destroy microorganisms

in human tissue. Pl. Opp. and Reply at 9-10.

The first of these arguments is easily disposed of: it presents a hypothetical that does not apply to Restasis or the resolution of the Allergan citizen petition. The hypothetical also has serious flaws. Since FDA has repeatedly demonstrated in this record that it might first approve a drug as a non-antibiotic and then, after further consideration, change that status to antibiotic, it is not clear at all that an initial approval of Restasis as a non-antibiotic, before NDAs from Sandoz, would continue after FDA received NDAs covering one or more uses of an immunosuppressant with higher concentrations of cyclosporine.[10]

The second argument has more weight but ultimately cannot succeed. Congress did not define "in dilute solution" or give any guidance as to what evidence FDA should consider in deciding whether a given chemical substance has the capacity to inhibit or destroy microorganisms (human clinical trials, *in vivo* animal studies, and/or *in vitro* studies). Dr. Ramsey's memorandum opined that FDA should not rely on *in vitro* testing because results from the laboratory cannot necessarily be correlated to results in human beings. *See* AR Tab 3. A court is ill-equipped to decide this scientific debate. *See Troy Corp.*, 120 F.3d at 283.

Faced with this ambiguity in the statute, FDA has articulated a reasonable interpretation of "in dilute solution" and concluded that it should be a concentration of the antibiotic drug substance that is expected to be found in human tissue when the drug is administered at any

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[10] Allergan argues also that FDA is arbitrary and unreasonable because it does not require microbiology tests on all drug products to determine whether their chemical substances have the capacity to inhibit or destroy microorganisms in dilute solution. *See* Pl. Opp. and Reply at 11-12. Whatever the merits of this argument, which FDA disputes, it is of no assistance to the classification of cyclosporine, the drug substance at issue here. Cyclosporine meets the definition of "antibiotic" drug as FDA has rationally interpreted it.

dose for which it has been proposed or approved. AR Tab 39 at 20-21, 24-26. In its response to Allergan's citizen petition, FDA explained why it considers such a clinically relevant concentration (as suggested by Sandoz)[11] to be the appropriate standard. *Id.* Having considered Dr. Ramsey's points about *in vitro* testing, FDA concluded that *in vitro* studies, *in vivo* animal studies, and *in vivo* human studies could all be used in its decisions about a drug's status. *See* AR Tab 39 at 26-28. "FDA is to be accorded deference when it is evaluating scientific data within its technical expertise." *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 216 (D.D.C. 1996) (rejecting a claim that *in vivo* testing was required). Deference in this area of FDA activities is the norm. *United States v. Rutherford*, 442 U.S. 544, 553-54 (1979); *Serono Labs.*, 158 F.3d at 1320; *Berlex Labs., Inc. v. FDA*, 942 F. Supp. 19, 25 (D.D.C. 1996). While its choice is not the only logical course it could have adopted, FDA's considered response to Allergan's citizen petition "claim[s] the merit of its writer's thoroughness, logic and expertness" and is entitled to deference. *Mead*, 533 U.S. at 235.

V. CONCLUSION

The complaint will be dismissed. FDA has properly interpreted and applied the statutory definition of "antibiotic" drug in determining that cyclosporine is an antibiotic. Cyclosporine is an antibiotic drug approved by FDA before the passage of FDAMA. Drugs

[11] Allergon asserts that FDA's interpretation of "in dilute solution" should be given no deference because it was originally suggested by Sandoz. Pl. Opp. and Reply at 3-5. FDA intimates that it did not rely on Sandoz for the definition. Defs.' Reply at 13 n. 9. It would be to the agency's credit if it accepted a sensible and scientifically valid suggestion from a NDA applicant; it is the FDA's position that matters, not its original source.

containing cyclosporine, such as Restasis, are therefore exempt from the benefits and protections of Hatch-Waxman.

DATE: January 19, 2005.

/s/
ROSEMARY M. COLLYER
United States District Judge